REMARKS

Reconsideration is respectfully requested in light of the foregoing amendments and remarks that follow. Claims 1-3, 22 and 23 are pending. Claims 2, 3, 22 and 23 have been cancelled. Claims 44-48 have been added. New claim 44 is supported on page 44, lines 14-15. New claims 45 and 47 represent claim 22 in rewritten form for clarity; new claims 46 and 48, directed to a kit, are supported on page 32, line 38-page 33, line 2. Reference to prostate cancer is found throughout the specification. No new matter has been added and entry of the amendment is respectfully requested.

Claims 4-21 and 24-43 have been canceled as directed to a non-elected invention without prejudice to their prosecution in divisional applications

The Invention

The invention as presently claimed is directed to compositions designed to induce immunological response to prostate tumors, where these tumors and normal prostate express STEAP-2 protein. The claims by their terms are directed to tissues that express this protein, and evidence for this expression, as will be explained further below, is found in prostate tissue -- normal and cancerous. The assertion that the claimed composition targets both normal prostate and cancerous prostate tissue is inconsequential from a utility perspective due to the fact that the prostate is a nonessential organ. *See* Spitler, SE, et al., US Patent No. 5,925,362 (claiming vaccines,.using or stimulating prostate-specific antigen (PSA), capable of eliciting an immune antitumor response). "Thus, prostate cancer offers a unique opportunity for treatment with vaccines which characterize the host organ itself, rather than the malignant or metastatic nature of the cells per se." *Id.* at column 2, lines 41-44. Additionally, as discussed below, the present specification fully supports the composition claims as they relate to prostate cancer.

Claims to the protein fragments (2), modified forms (3) and the claim directed to a vaccine utilizing fragments of the STEAP-2 protein (claim 23) have been canceled. It is believed that the amendments to the claims, therefore, considerably simplify prosecution.

The substantive rejections which remain are addressed specifically below.

The Rejection Under 35 U.S.C. § 112, paragraph 2; Indefiniteness

Claims 22-23 were rejected under 35 U.S.C. § 112, paragraph 2, for indefiniteness. Claim 22 was re-written in response to the Examiner's suggestions as claim 44 and is now in acceptable form and claim 23 was cancelled. Therefore the basis for this rejection is rendered moot.

The Rejection Under 35 U.S.C. § 112, paragraph 1; Undue Experimentation

Claims 1-3, and 22-23 were rejected under the first paragraph of 35 U.S.C. § 112 as not enabled by the specification. Claims 2, 3, 22 and 23 have been cancelled; claim 22 has been replaced by claim 44. In one aspect, the basis for this rejection appears to reside in an asserted lack of a credible utility because the specification putatively does not provide guidance or working examples to predict efficacy. This is not the function of the specification. The function of the specification is to teach how to make and use the invention, and this is clearly taught.

As to specific directions for use in treatment, optimization of dosage and administration are routine matters of routine experimentation once the active ingredient is identified, as it has been here. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *See In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976); MPEP § 2164.01. Experimentation may not be considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation -- time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See id.*; MPEP § 2164.06. Specific formulations and routes of administration are readily determined through routine experimentation. The references discussed below support this assertion.

A. Inducing an Immunological Response to Cancer

The first objection is that the teachings of the specification do not provide enough guidance for one skilled in the art to make or use the claimed immunological compositions for "activity [sic] immunotherapy in humans." The Office cites Gura (1997) which is directed, not to immunological compositions, but rather to anticancer drugs in general. This document describes systems of cancer drug identification, not relevant here, that have many challenges.

The article focuses on two primary screening methods: clonogenic assays and xenografts. It is well taken that there are problems relating to extrapolating *in vitro* results to *in vivo* efficacy and that animal models are not a perfect representation of predicted efficacy in humans, but that is both well-known and not the point of the article. It is not necessary to provide results in humans in order to support utility. *See, In re Brana*, 34 USPQ2d 1437 (Fed. Cir. 1995). The *Brana* court stated that the role of assessment of effectiveness of certain compounds in treating humans is placed in the hands of the FDA, and "FDA approval . . . is not a prerequisite for finding a compound useful." *Id.* at 1442. In any event, the present invention does not relate to anticancer drugs of the type discussed in Gura.

More relevant to the presently pending claims are Bellone (1999) and Spitler (1995). The Spitler reference was cited as a general overview of the state of the art in cancer vaccines. The problem with the reference as used in the present application is that it describes the state of the art as it was in 1995. Much has occurred in the art between 1995 and the priority date of the present application. It should also be noted that Spitler is not truly pessimistic towards the outlook of cancer vaccines, presenting an overview of the failures of the old, and going on to describe the promising futures of the new. In fact, one of the named inventors of US Patent No. 5,925,362 (discussed above and below), which presents claims to a vaccine composition against cancer, is the same person, LE Spitler, as the author of the article discussed above.

The Bellone reference was used to indicate that there was a "poor correlation between induction of specific T-cells and clinical responses." The article describes various disadvantages of using synthetic peptides as vaccines as well. However, the article also outlines both the reasons for, and solutions to, the problem of "poor correlation." One of these reasons is clinical trial design. The article goes on to point out a major flaw in previous clinical trial designs and describes a potential solution to these problems that "should ensure a more potent and efficient tumor specific immunity." *Id.* at page 459. One such improvement in trial and vaccine design is described in Ossendorp et al., ((1998) J. Exp. Med., 187: 693-702). As to the disadvantages of using synthetic vaccines, the Bellone article is not completely negative on that front and proposes a couple of solutions which would increase efficacy and reduce potential adverse side effects in patients.

In any event, a general teaching that not all promising candidates for anticancer vaccines necessarily will be effective is not sufficient to cast doubt on the credibility of the present invention. Additionally, they certainly do not indicate that it would be impossible to utilize the appropriate immunogen to elicit an appropriate response.

The presently claimed invention provides compositions which induce an immunological response to prostate cancer. The claimed protein is expressed in both normal and cancerous prostate tissue. For example, Applicants respectfully direct the Examiner's attention to Example 6. This example indicates expression analysis of STEAP-2 mRNA. Specifically, Example 6A (which references Figures 14 and 15) describes STEAP-2 mRNA expression in normal prostate tissue versus other human tissues as evidenced through Northern blotting and RT-PCR. Panel A of Figure 14 indicates that STEAP-2 mRNA expression is found in normal and LAPC prostate cancer xenografts. Panel B of Figure 14 indicates STEAP-2 mRNA prostate-specific expression after 25 cycles of amplification with lower level expression in other normal human tissues witnessed only after increased amplification (30 cycles). In Figure 15 evidence is provided for expression of STEAP-2 mRNA in normal prostate and prostate cancer xenografts determined by Northern blot analysis. The prostate cancer xenograft is an art recognized animal model for human prostate cancer that uses tumor tissuc from human prostate cancer patients. The data in Figure 15 indicate that STEAP-2 polypeptides and proteins are most likely expressed in human prostate tissues but not in a variety of other normal human tissues. This evidence indicates that STEAP-2 expression is highly prostate-specific.

As discussed above, the present claims encompass an invention with sufficient utility. The reference to the Spitler patent (see above) bolsters this assertion. Claims in the Spitler patent are directed to eliciting an antitumor immune response to prostate tumors where the active ingredient elicits an immune response to PSA. *See* US Patent No. 5,925,362, claim 1. Logically, the response could not be limited to the tumors themselves, rather, as the invention acknowledges, they are directed at attacking the entire prostate. As the prostate gland is not an essential organ this treatment both attacks prostate cancer specifically and avoids adverse health impacts cause by nonspecific treatment. The present claims are directed to a similar mechanism of action and encompass a similar prostate-specific composition for inducing an immunological response thereto.

B. Marker for Cancer Diagnosis

It is acknowledged by the Office that mRNA encoding the presently claimed polypeptide is expressed in both normal and cancerous prostate tissue. The instant claims are directed to inducing an immunological response to prostate tissue expressing STEAP-2 polypeptide rather than providing a marker or target. This is the utility of the claimed STEAP-2.

Although the objection itself is not germane to the present claims, one aspect of this objection (the concept that although mRNA levels may be upregulated, protein levels may not) must be addressed. Respectfully, applicants believe that this assertion is entirely too general. As argued below, while the correlation between mRNA expression and protein expression may not be perfect, it does exist. Clearly, if there is no mRNA, there can be no protein. The existence of high levels of mRNA is quite probative evidence that protein will be produced.

Shantz (1999), Fu (1996), McClean (1993), and Alberts (1994 (citing an article from 1988)) are cited as support for the general assertion that a gene can be regulated at different levels and not all mRNAs express as proteins. Fu was specifically directed to examining translational regulation of p53 gene expression in AML patients, and concluded that it might be possible that binding factors acting on the p53 3'UTR may regulate p53 mRNA translation *in vivo*. Shantz investigated translational regulation of ornithine decarboxylase and concluded that the upstream ORF in 5'UTR of AdoMetDC mRNA may cause ribosome stalling, thus decreasing the efficiency of protein translation. McClean indicates that one of the reasons for protein over-expression witnessed in irradiated hamster ovary cells was due to protein stability compared with Pgp mRNA instability. Alberts indicates that the levels of ferritin and transferrin receptor protein translation are dependent on iron concentrations which are purported to affect the stability of mRNA. There is a reverse, but predictable, correlation between iron concentrations in the cytosol and translation of the ferritin and transferrin receptor proteins.

Two things need to be stated regarding the above disclosures. First, in all cases except that of Alberts, protein is actually produced, even if not at levels that correlate quantitatively with mRNA levels. The sole exception, Alberts, is an entirely unique situation where an external factor related to the protein itself, iron, as one might expect, exerts an effect. Second, with regard to the usefulness of the peptide of the invention, the above correlation is entirely

unnecessary. All that is required is that sufficient levels of the protein be present to subject the tissue to immunological attack. As the first three documents cited by the Office clearly show, protein will be present when mRNA is present, even if the amounts do not perfectly correlate. Thus, the cited documents merely support the assertion that gene expression may be regulated at levels of both transcription and translation, and verify the general rule mRNA and protein produced are generally present together.

C. Fragments of the STEAP-2 Polypeptide

The third objection is directed to fragments of STEAP-2 polypeptide. The Applicants appreciate the acknowledgement by the Examiner of the enablement of the presently claimed polypeptide; however, in light of the cancellation of the claims directed to fragments and modified forms thereof (claims 2, 3, and 23), the basis of this rejection is rendered moot.

D. Enablement - Isolated Polypeptide

Claims 2-3 and 23 were rejected under 35 USC 112, first paragraph, for the same reasons as the objection under subsection (C) discussed above. As this rejection involves the same cancelled claims, the basis of this rejection is rendered moot.

Rejection under 35 U.S.C. § 102(e)

Claim 2 was rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Lal *et al.*, US Patent No. 6,048,970. This claim has been cancelled without prejudice to further prosecution.

CONCLUSION

It is believed that claims 1, 44-48 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this request and the Patent Office determines that a fee is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952, ref. Docket No. 511583001720**.. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: October 12, 2001

By Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

Version with markings to show changes made.

IN THE SPECIFICATION

Kindly amend to specification as follows:

Please substitute the following paragraph for the paragraph starting on line 17 of page 7:

--Fig. 11A. Amino acid sequence alignment of STEAP-1 (8P1D4 clone 10; SEQ ID NO:2), STEAP-2 (98P4B6 clone GTD3; SEQ ID NO:6), STEAP-3 (98P4B6 clone GTD3; SEQ ID NO:8), and STEAP-4/R80991 (SEQ ID NO:13) [STEAPs 1-4] using PIMA program (PIMA 1.4 program available at Internet address: [<]http:\\dot.imgen.bcm.tmc.edu:9331\multi-align\multi-align.html[>]); transmembrane domains identified by the SOSUI program (available at Internet address [<]http:\\www.tuat.ac.jp\~mitaku\adv_sosui\submit.html[>]) are in bold. PIMA maximal linkage clustering results shown; identical residues shown in bold.--

Pleasc substitute the following paragraph for the paragraph starting on page 7, line 23:

--FIG. 11B. Amino acid sequence alignment of STEAP-1 (8P1D4 clone 10; portion of SEQ ID NO:1) and STEAP-2 (98P4B6 clone GTD3; portion of SEQ ID NO:6) sequences. The alignment was performed using the SIM alignment program of the Baylor College of MEdicine Search LAuncher Web site. Transmembrane domains are indicated in boldface. The results show a 54.9% identity in a 237 residues overlap (Score 717.0; Gap frequency:0.0%).--

Please substitute the following paragraph for the paragraph starting on page 7, line 29:

--FIG 11C. Amino acid sequence alignment of STEAP-1 (portion of SEQ ID NO: 2) and STEAP-3 (98P4B6 clone GTD3; portion of SEQ ID NO:8) sequences. Identical residues indicated with asterisks. SIM results: 40.9% identity in 264 residues overlap; Score 625.0; Gap frequency: 0.0%.--

Please substitute the following paragraph for the paragraph starting on page 7, line 33:

--FIG 11D. Amino acid sequence alignment of STEAP-2 (portion of SEQ ID NO: 6) and STEAP-3 (98P4B6 clone GTD3; portion of SEQ ID NO:8) sequences. Identical

residues indicated with asterisks. SIM results: 47.8% identity in 416 residues overlap; Score 1075.0; Gap frequency: 0.2%.--

Please substitute the following paragraph for the paragraph starting on page 8, line 37, spanning pages 8-9:

--FIG. 12. Expression of STEAP-3 mRNA in normal tissues by Northern blot (FIG. 12A) and RT-PCR (FIG. 12B). For RT-PCR analysis, first strand cDNA was prepared from 16 normal tissues. Normalization was performed by PCR using primers to actin and GAPDH. Semi-quantitative PCR, using primers to AI139607, shows predominant expression of AI139607 in placenta and prostate after 25 cycles of amplification. The following primers were used to amplify AI139607:

AI139607.1	5' TTAGGACAACTTGATCACCAGCA 3'	(SEQ ID NO: 16)
AI139607.2	5' TGTCCAGTCCAAACTGGGTTATTT 3'	(SEQ ID NO: 17)--

Please substitute the following paragraph for the paragraph starting on page 9, line 7:

--FIG. 13. Predominant expression of STEAP-4/R80991 in liver. First strand cDNA was prepared from 16 normal tissues. Normalization was performed by PCR using primers to actin and GAPDH. Semi-quantitative PCR, using primers to R80991, shows predominant expression of R80991 in liver after 25 cycles of amplification. The following primers were used to amplify R80991:

R80991.1	5' AGGGAGTTCAGCTTCGTTCAGTC 3'	(SEQ ID NO: 18)
R80991.2	5' GGTAGAACTTGTAGCGGCTCTCCT 3'	(SEQ ID NO: 19)--

Please substitute the following paragraph for the paragraph starting on page 9, line 14:

--FIG. 14. Predominant expression of STEAP-2 (98P4B6) in prostate tissue. First strand cDNA was prepared from 8 normal tissues, the LAPC xenografts (4AD, 4AI and 9AD) and HeLa cells. Normalization was performed by PCR using primers to actin and GAPDH. Semi-quantitative PCR, using primers to 98P4B6, shows predominant expression of 98P4B6 in normal prostate and the LAPC xenografts. The following primers were used to amplify STEAP II:

98P4B6.1	5' GACTGAGCTGGAACTGGAATTTGT 3'	(SEQ ID NO: 20)
98P4B6.2	5' TTTGAGGAGACTTCATCTCACTGG 3'	(SEQ ID NO: 21)--

Please substitute the following paragraph for the last full paragraph on page 36

--To determine expression levels of the 8P1D4 gene, 5 μl of normalized first strand cDNA was analyzed by PCR using 25, 30, and 35 cycles of amplification using the following primer pairs, which were designed with the assistance of (MIT[; for details, see, www.genome.wi.mit.edu]):--

Please substitute the following paragraph for the paragraph starting on page 40, line 9:

--A 15 mer peptide corresponding to amino acid residues 14 through 28 of the STEAP-1 amino acid sequence as shown in FIG. 1A (WKMKPRRNLEEDDYL (portion of SEQ ID NO: 2)) was synthesized and used to immunize sheep for the generation of sheep polyclonal antibodies towards the amino-terminus of the protein (anti-STEAP-1) as follows. The peptide was conjugated to KLH (keyhole limpet hemocyanin). The sheep was initially immunized with 400 (g of peptide in complete Freund's adjuvant. The animal was subsequently boosted every two weeks with 200 (g of peptide in incomplete Freund's adjuvant. Anti-STEAP antibody was affinity-purified from sheep serum using STEAP peptide coupled to affi-gel 10 (Bio Rad). Purified antibody is stored in phosphate-buffered saline with 0.1% sodium azide.--

Please substitute the following paragraph for the paragraph starting on page 41, line 3:

--To determine the extent of STEAP-1 protein expression in clinical materials, tissue sections were prepared from a variety of prostate cancer biopsies and surgical samples for immunohistochemical analysis. Tissues were fixed in 10% formalin, embedded in paraffin, and sectioned according to standard protocol. Formalin-fixed, paraffin-embedded sections of LNCaP cells were used as a positive control. Sections were stained with an anti-STEAP-1 polyclonal antibody directed against a STEAP-1 N-terminal epitope (as described immediately above). LNCaP sections were stained in the presence of an excess amount of the STEAP-1 N-terminal peptide immunogen used to generate the polyclonal antibody (peptide 1) or a non-specific peptide derived from a distinct region of the STEAP-1 protein (peptide 2; YQQVQQNKEDAWIEH (SEQ ID NO: 30)).--

Please substitute the following paragraph for the second full paragraph on page 44:

--The STEAP-2 [STRAP-2] cDNA (98P4B6-GTD3) contains a 355 bp 5'UTR (untranslated region) that is 72% GC rich, suggesting that it contains translational regulatory elements. The cDNA encodes an open reading frame (ORF) of 454 amino acids (a.a.) with six potential transmembrane domains. This is in contrast to STEAP [STRAP], which is 339 a.a. in length. Alignment with STEAP-1 [STRAP-1] demonstrates 54.9% identity over a 237 amino acid overlap. Interestingly, the locations of the six putative transmembrane domains in STEAP-2 [STRAP-2] coincide with the locations of the transmembrane domains in STEAP-1 [STRAP-1] (see alignment). The homology of STEAP-2 [STRAP-2] with STEAP-1 [STRAP-1] is highest in the regions spanned by the first putative extracellular loop to the fifth transmembrane domain. This analysis and the sequence of STEAP-2 [STRAP-2] suggest some significant differences between STEAP-1 [STRAP-1] and STEAP-2 [STRAP-2]: STEAP-2 [STRAP-2] exhibits a 205 a.a. long intracellular N-terminus (compared to 69 a.a. in STEAP-1 [STRAP-1]) and a short 4 a.a. intracellular C-terminus (compared to 26 a.a. in STEAP-1 [STRAP-1]). These differences could imply significant differences in function and/or interaction with intracellular signaling pathways. To identify a unique mouse EST corresponding to STEAP-2 [STRAP-2], the unique N-terminus of STEAP-2 [STRAP-2] was used to query the dbest database. One EST mouse EST was isolated (AI747886), mouse kidney) that may be used in the identification of mouse STEAP-2 [STRAP-2]and in expression analysis of STEAP-2 [STRAP-2] in mouse.--

Please substitute the following lines for the lines starting on page 46, lines 20-22:

--The following PCR primers were used for STEAP-1:

8P1D4.1	5' ACTTTGTTGATGACCAGGATTGGA 3'	(SEQ ID NO:14)
8P1D4.2	5' CAGAACTTCAGCACACACAGGAAC 3'	(SEQ ID NO:15)--

Please substitute the following lines for the lines starting on page 46, lines 30-32:

--The following PCR primers were used for 98P4B6/STEAP-2:

98P4B6.1	5' GACTGAGCTGGAACTGGAATTTGT 3'	(SEQ ID NO:20)
98P4B6.2	5' TTTGAGGAGACTTCATCTCACTGG 3'	(SEQ ID NO:21)--

Please substitute the following lines for the lines starting on page 47, lines 1-3:

--The following PCR primers were used for AI139607:

AI139607.1 5' TTAGGACAACTTGATCACCAGCA 3' (SEQ ID NO:16)

AI139607.2 5'TGTCCAGTCCAAACTGGGTTATTT3' (SEQ ID NO:17)--

Please substitute the following lines for the lines starting on page 47, lines 10-12:

--The following PCR primers were used for R80991:

R80991.3 5' ACAAGAGCCACCTCTGGGTGAA 3' (SEQ ID NO:33)

R80991.4 5' AGTTGAGCGAGTTTGCAATGGAC 3' (SEQ ID NO:34)--

Please Substitute the following two tables for the tables on page 49:

STEAP-1 (SEQ IN NO: 2)			
Rank	Start Position	Subsequence Residue Listing	Score (Estimate of Half Time of Disassociation of Molecule Containing This Subsequence)
1	165	GLLSFFFAV (portion of SEQ ID NO:2)	10776.470
2	86	FLYTLLREV (same)	470.951
3	262	LLLGTIHAL (same)	309.050
4	302	LIFKSILFL (same)	233.719
5	158	MLTRKQFGL (same)	210.633

STEAP-2 (SEQ ID NO: 6)			
Rank	Start Position	Subsequence Residue Listing	Score (Estimate of Half Time of Disassociation of Molecule Containing This Subsequence)
1	227	FLYSFVRDV (portion of SEQ ID NO:6)	1789.612
2	402	ALLISTFHV (same)	1492.586
3	307	LLSFFFAMV (same)	853.681
4	306	GLLSFFFAM (same)	769.748
5	100	SLWDLRHLL (same)	726.962